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ASSESSMENT OF NEUROLOGICAL EFFECTS OF DRUGS ON OCULOMOTOR  
AND VISUAL FUNCTION IN THE PRIMATE

Annual Summary Report

E. Gregory Keating, Ph.D.  
Professor of Anatomy  
S.U.N.Y. Upstate Medical Center  
Syracuse, New York 13210

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The research assesses the effects of cholinergic drugs on the eye movements of monkeys engaged in visual search and tracking tasks. The tasks mimic skills of general utility to military personnel in the field. To date, normal patterns of eye movements have been defined and there are preliminary results describing the effects of physostigmine (.025-.075 mg/K), and pralidoxime (1-16 mg/K). Only the highest dose of physostigmine consistently degraded visual search. Even then the effect was a subtle one and was primarily oculomotor in character rather than sensory, cognitive or motivational. Pra-		

20. Abstract (continued)

lidoxime also had no consistent effect except at the highest dose of 16 mg/K. Testing was erratic at this dose. Visual search was successful when attempted at all by the monkey suggesting a motivational rather than specifically oculomotor effect from this drug.

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### Summary

A number of cholinergic agents are deemed useful as prophylactics or antidotes to organophosphate poisoning yet have their own toxic effects. Dosages of these agents which are known to not grossly disrupt behavior may nonetheless degrade performance of sophisticated tasks required of the personnel of a modern mechanized army.

The contract uses on animal model (primate) to assess the effects of cholinergic drugs on the performance of visual search and tracking tasks which mimic skills generally used in the field.

The eye movements of cynomolgous monkeys (*Macaca fascicularis*) were recorded with the magnetic search coil technique while they searched for camouflaged visual targets. To date the research has defined the normal patterns of eye movements of monkeys engaged in visual search and there are preliminary results describing the effects of physostigmine (.025 - .075 mg/K) and pralidoxime (1 - 16 mg/K). Only at the highest dose of .075 mg/K did physostigmine consistently degrade eye movements and impair visual search. The deficit was a subtle one and was primarily an oculomotor effect rather than a motivational, visual, or cognitive impairment. Pralidoxime also had no consistent effect at any but the highest dose of 16 mg/K. Behavioral testing was erratic at this dose but visual search was successful when attempted at all by the monkey, suggesting a motivational rather than specifically oculomotor impairment.

*regarding therapeutic agents; chemical warfare; therapy*  
*inhibitors; (K+)*  
Foreword

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978.

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### Methods of Research

The following annual progress report is submitted in compliance with the terms of our contract "Assessment of Neurological Effects of Drugs on Oculomotor and Visual Function in the Primate." The report covers the first year of the contract.

Our purpose is to develop an animal model (primate) for visual search and target tracking performance so as to assess the behavioral effects of cholinergic drugs (e.g., atropine, pralidoxime, physostigmine, pyridostigmine). Two tasks have been developed to mimic the visual search and tracking skills required of military personnel in the field. A search task requires the monkey to find and fixate a target spot embedded in a field of distractors. A second tracking task not yet completed requires the monkey to track and predict the trajectory of a moving target. We use the magnetic search coil technique to record the monkeys' eye movements during the tasks. The data provide indices of basic visual and oculomotor competence as well as measures of more cerebral or attentional decrements caused by cholinergic agents.

During the past quarter, drug trials with the visual search test continued with cynomolgous monkeys (Macaca fascicularis). The schedule of completed drug trials is shown in Table 1.

Table 1

Pralidoxime (A=1; B=2; C=4; D=Saline; E=8; F=16 mg/K)

Subject 1	B D C C C B D D A E E A# A
Subject 2	D C C E E B D A B# A B
Subject 3	A# A D B D B C E C E F F
Subject 4	C# A D B C A E B E D F F

Physostigmine (A=.025; B=.050; C=.075 mg/K)

Subject 1	D A B B A D C C
Subject 2	B D B C D A C A
Subject 3	D C B A A D C B# B
Subject 5	D D C C# A A B B

Atropine (A=.014; B=.045; C=.14; D=Saline; E=.25 mg/K)

Subject 1	D C A E D
Subject 2	C C B A E

# technical imperfections invalidate data

Data from the pralidoxime and physostigmine trials have been analyzed. This progress report includes for each of these drugs a summary of any observed neurological effects, description of oculomotor changes as characterized by strip-chart recordings of the eye movement traces supported by quantified changes in certain oculomotor parameters, and finally, graphs of performance on the Visual Search test. Performance on visual search is expressed as "z scores" in which the monkeys' behavior under the influence of the drug is normalized to the mean and variation of its baseline behavior. Specifically,

$$Z = \frac{X_D - M_B}{\sigma_B}$$

where,  $X_D$  = average performance over 72 trials of Visual Search on the day of the drug.

$M_B$  = mean performance over all of the baseline days (approx. 50 blocks of 36 trials each)  
 $\sigma_B$  = standard deviation of the baseline blocks

#### Results of Preliminary Analysis

Graphs show the results for three measures: percent of trials on which the monkey successfully fixated the target, the time, and the number of fixations that it took to fixate the target. Data were collected during an Early (15-25 minutes) and a Late (40-50 minutes) session after drug administration. Under the assumption that the "z scores" distribute normally, performance within  $Z = + 1.96$  is considered to represent the limits of normal behavior. In practice, our previous experience with this measure test is that reliable drug decrements on the Visual Search test are signalled by Z scores falling well outside these limits.

#### Physostigmine

##### .025 mg

No neurological nor oculomotor effects were observed. Visual Search performance was normal.

##### .050 mg

No neurological symptoms were noticed. The oculomotor record was mostly normal except that during the early session jitter occasionally appeared in the record when the monkey attempted to hold a fixation point.

Visual Search performance was generally normal but for a slight increase in the time required to find the target.

##### .075 mg

The neurological status was normal with no obvious muscle weakness, ptosis, vomiting, or pupillary signs. The monkeys appeared restless and worked their tongues and jaws in a swallowing movement characteristic of animals experiencing a dry mouth.

The oculomotor record had obvious changes at this dose that were more pronounced in the Early session. These appeared as jitter, fragmented fixations, and hypometric saccades that undershot the target. When hypometric, both the saccade and fixations fell short of the target. A pulse-step mismatch also occurred, the fixation (often modelled as a "step" of neuronal activity) falling somewhat shorter than the pulse or saccadic portion of the eye movement. The jittery fixations showed up quantitatively as increased drift in the fixations (e.g.  $32$  vs.  $21.6 \pm 0.6$ ; where  $32$  is the drug value, and  $21.6$  &  $0.6$  are the baseline mean and standard deviation, in radial minutes of visual angle).

Time to find the target increased and the number of targets acquired decreased inconsistently but these were subtle decrements in visual search. The monkeys tested without interruption throughout the drug session.

#### Pralidoxime

##### 1 & 2 mg

No neurological symptoms nor oculomotor abnormalities appeared. Performance on Visual Search was normal.

##### 4 mg

Neurological status was normal. Excessive blinking occasionally increased the number of spikes in the vertical channel of the eye record, but oculomotor competence was mostly normal. Performance of visual search was unaffected.

##### 8 mg

Neurological status was normal. The oculomotor record revealed some drift in fixations. The monkeys had difficulty extending their fixations to the outer targets. The deficit appeared as early as 4 minutes after injection and made it difficult to achieve an accurate calibration. During testing, some undershooting of targets appeared in the analysis (60' vs. 26  $\pm$  3') but this deficit may be underestimated by the skewed calibrations.

Only one animal's success in finding visual targets was impaired by this dose.

##### 16 mg

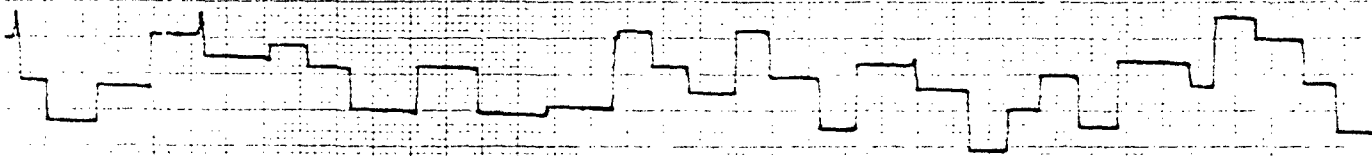
The neurological and oculomotor status was as described for the 8 mg/K dose.

Testing was erratic and intermittent and this was reflected in a reduced percentage of successful trials in one of the two subjects thus far tested at this dose. However, on successful trials the targets were fixated within the normal amount of time and number of fixations.

#### Atropine

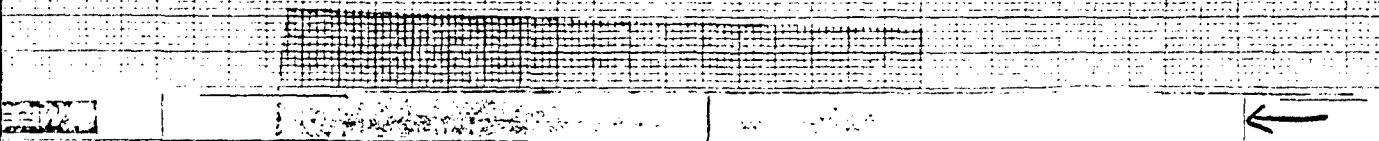
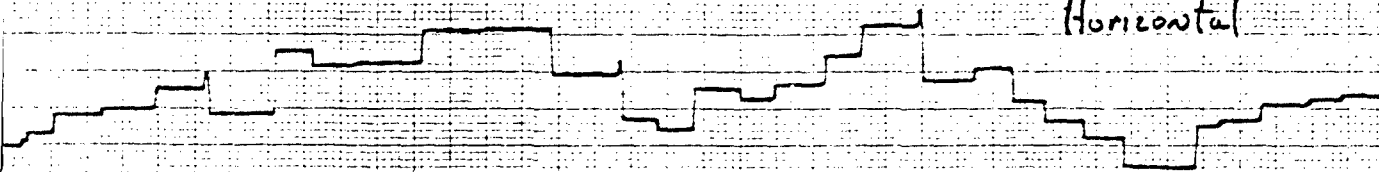
There are insufficient data to review at this time.

Vertical

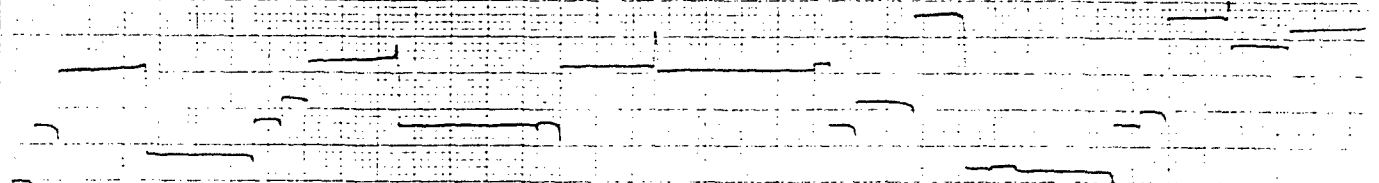


Saline

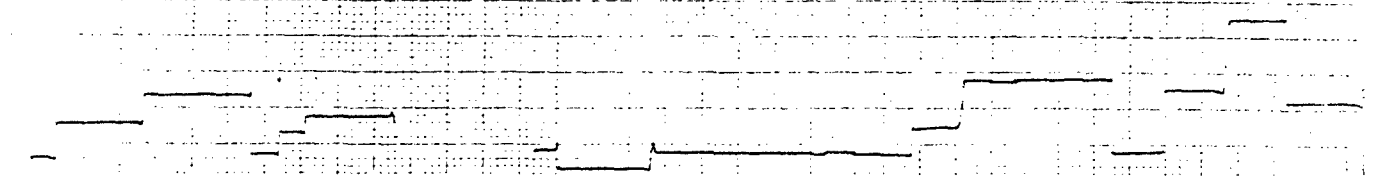
Horizontal



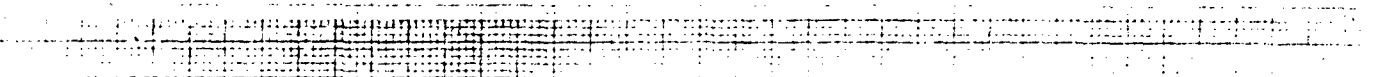
Vertical



Physostigmine .075 mg/K



Horizontal



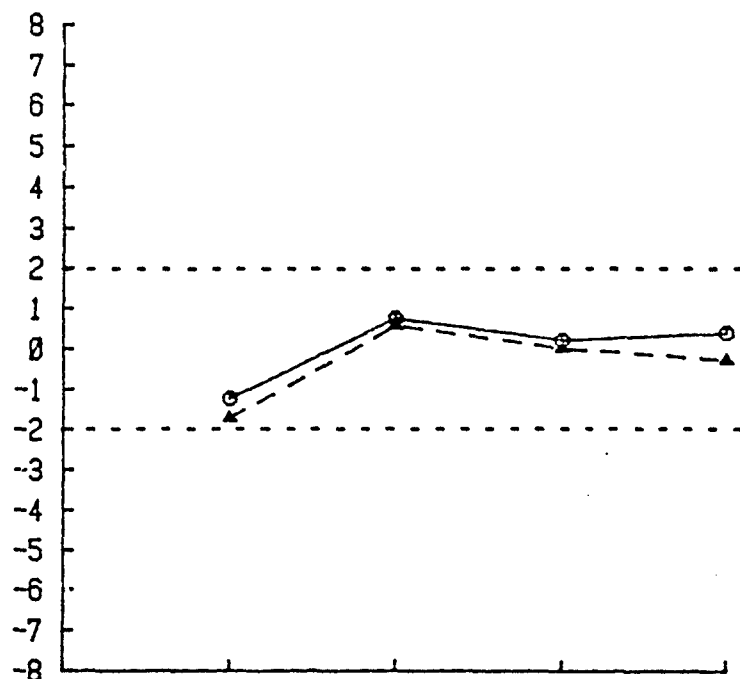


PHYSOSTIGMINE  
PERCENT OF TARGETS FIXATED

▲ - - - - ▲ EARLY  
○ - - - - ○ LATE

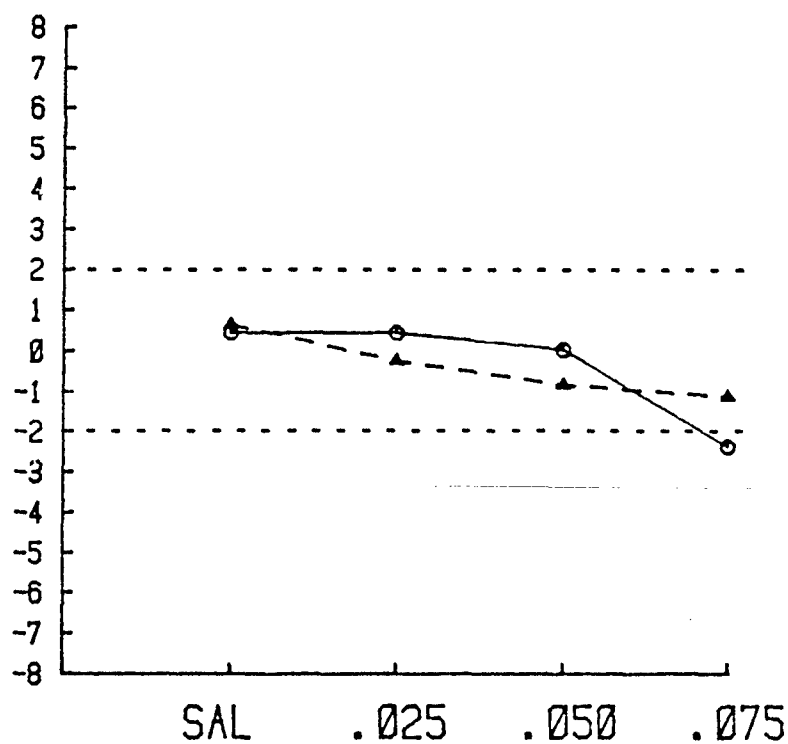
SUBJECT 1

Z SCORE



SUBJECT 2

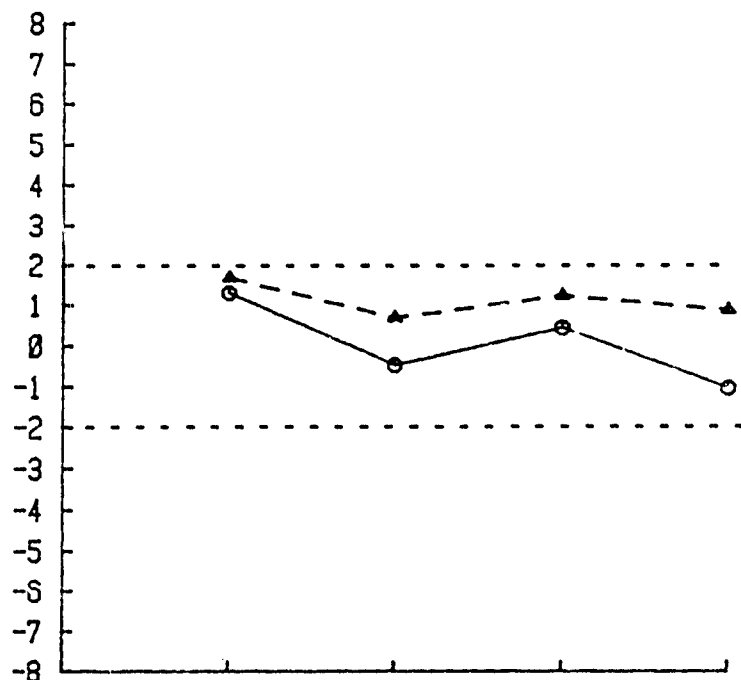
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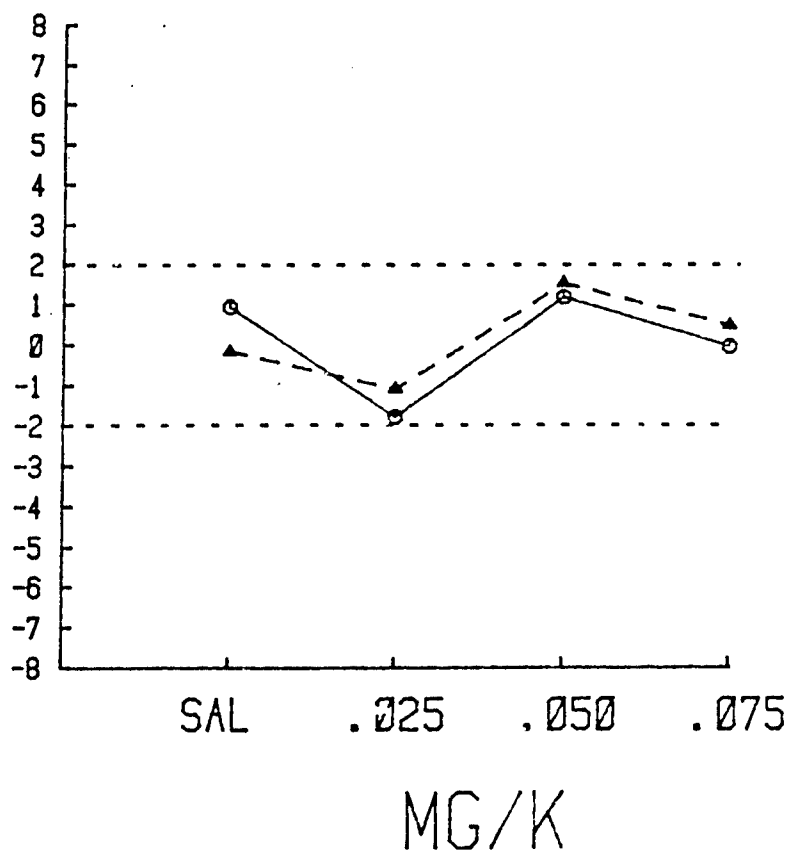
PHYSOSTIGMINE  
NUMBER OF FIXATIONS TO FIND TARGET

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○ - - - - ○ LATE

SUBJECT 1



SUBJECT 2

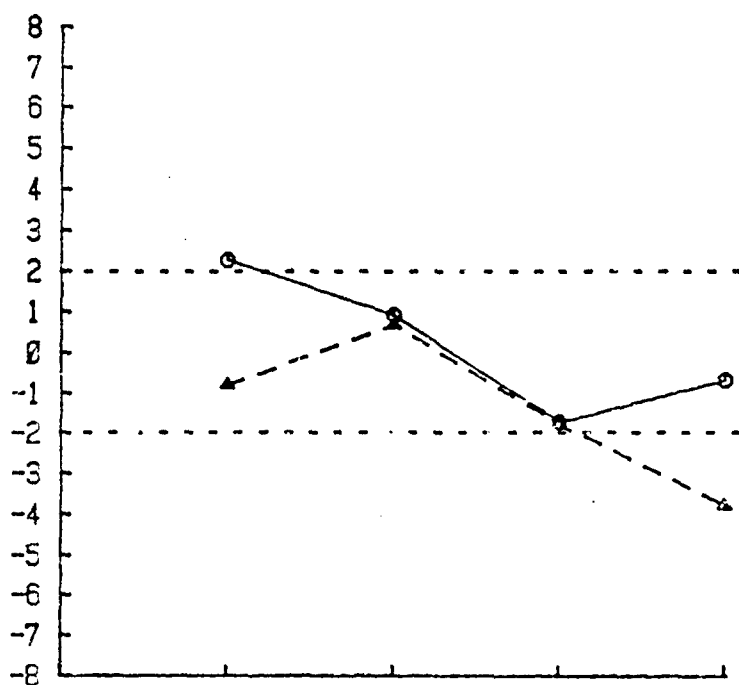


PHYSOSTIGMINE  
PERCENT OF TARGETS FIXATED

▲ - - - - ▲ EARLY  
○ - - - - ○ LATE

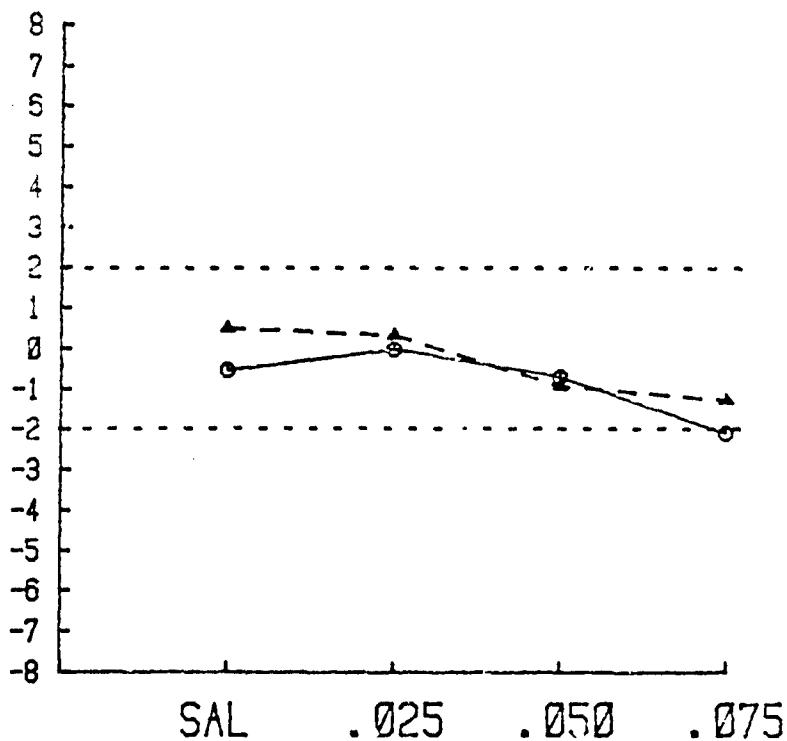
SUBJECT 3

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SUBJECT 5

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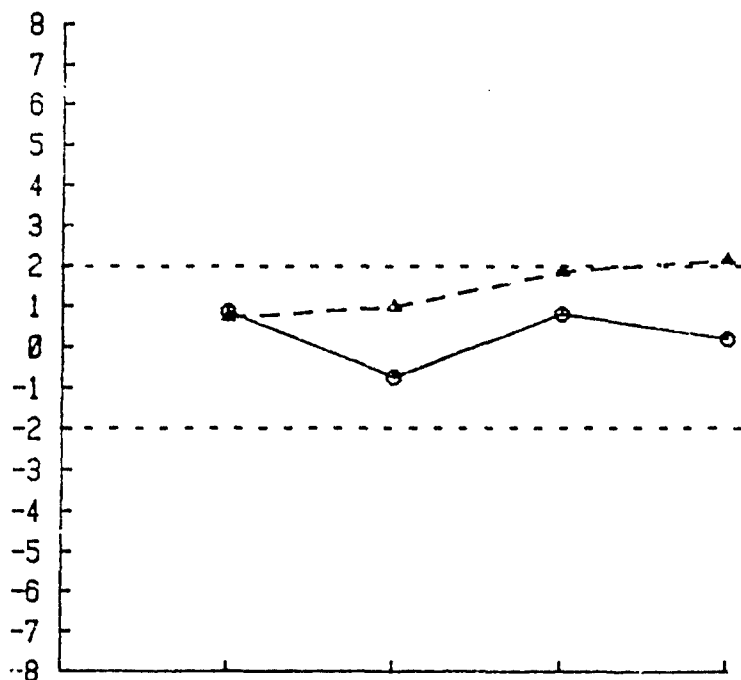
MG/K

PHYSOSTIGMINE  
TIME TO FIXATE TARGET

▲ - - - - ▲ EARLY  
○ - - - - ○ LATE

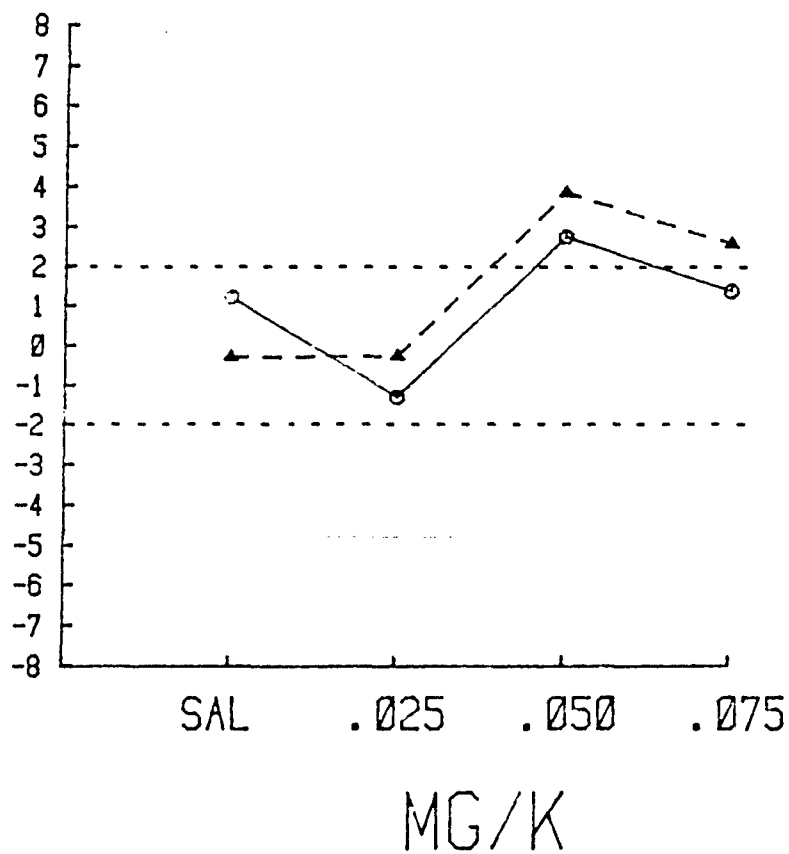
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE



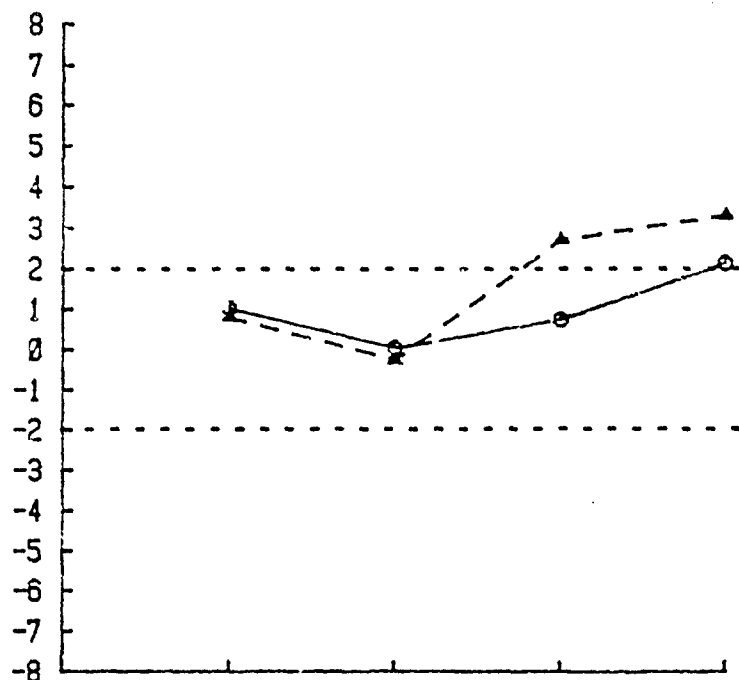
# PHYSOSTIGMINE TIME TO FIXATE TARGET

▲ - - - - - EARLY

○ - - - - - LATE

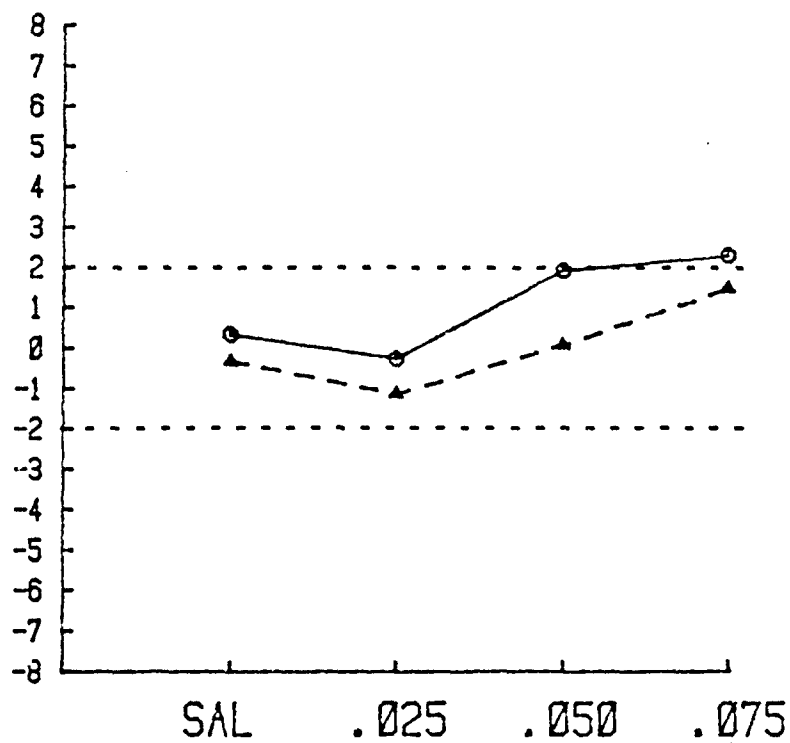
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Z SCORE



SUBJECT 5

Z SCORE

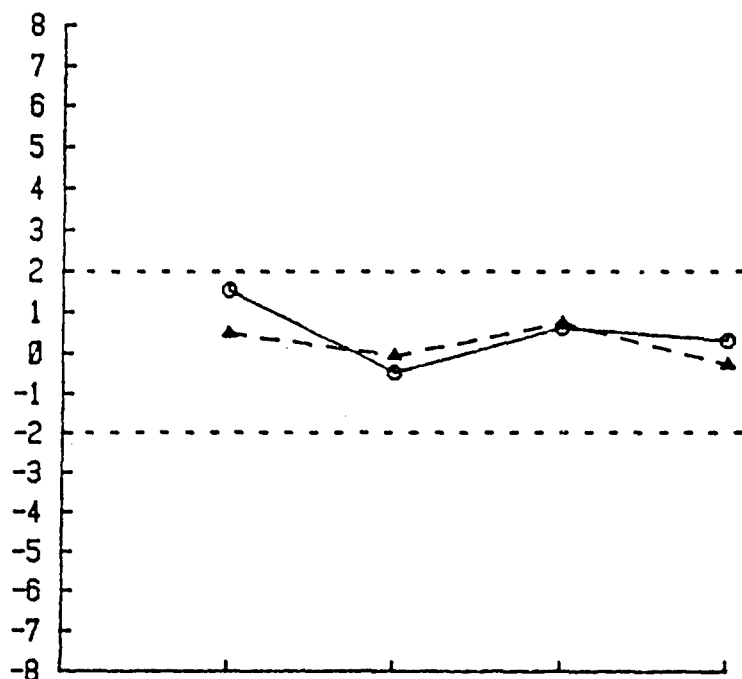


PHYSOSTIGMINE  
NUMBER OF FIXATIONS TO FIND TARGET

△ - - - - △ EARLY  
○ - - - - ○ LATE

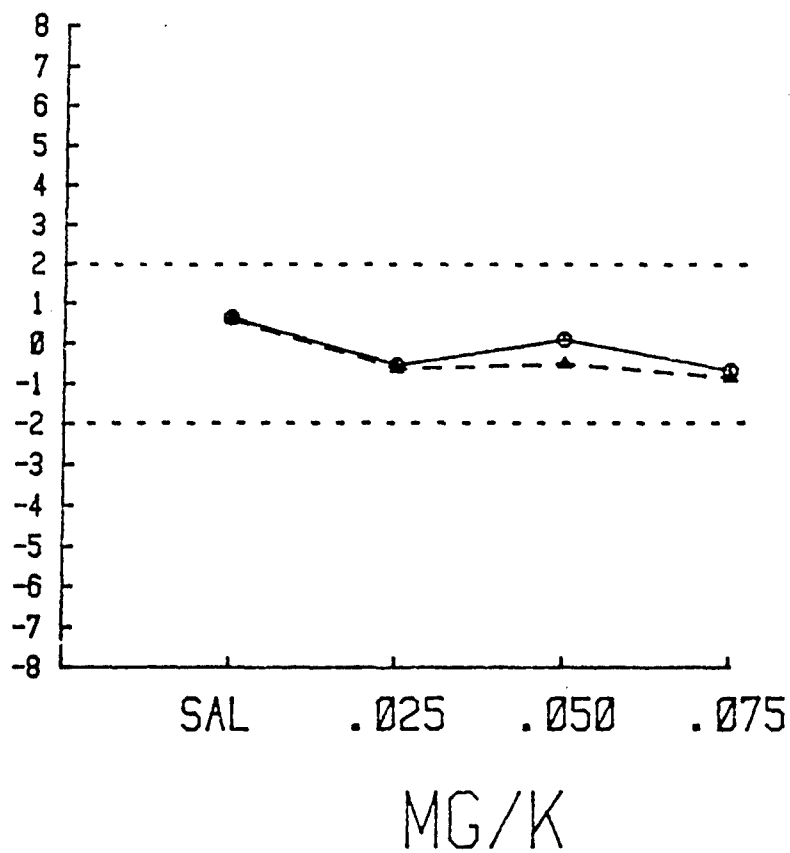
SUBJECT 3

Z SCORE



SUBJECT 5

Z SCORE



OCULOMOTOR -- PRALIDOXIME

SALEM, NH. U.S.A.

Vertical

SALEM, NH. U.S.A.

Saline

Horizontal

Vertical

Pralidoxime

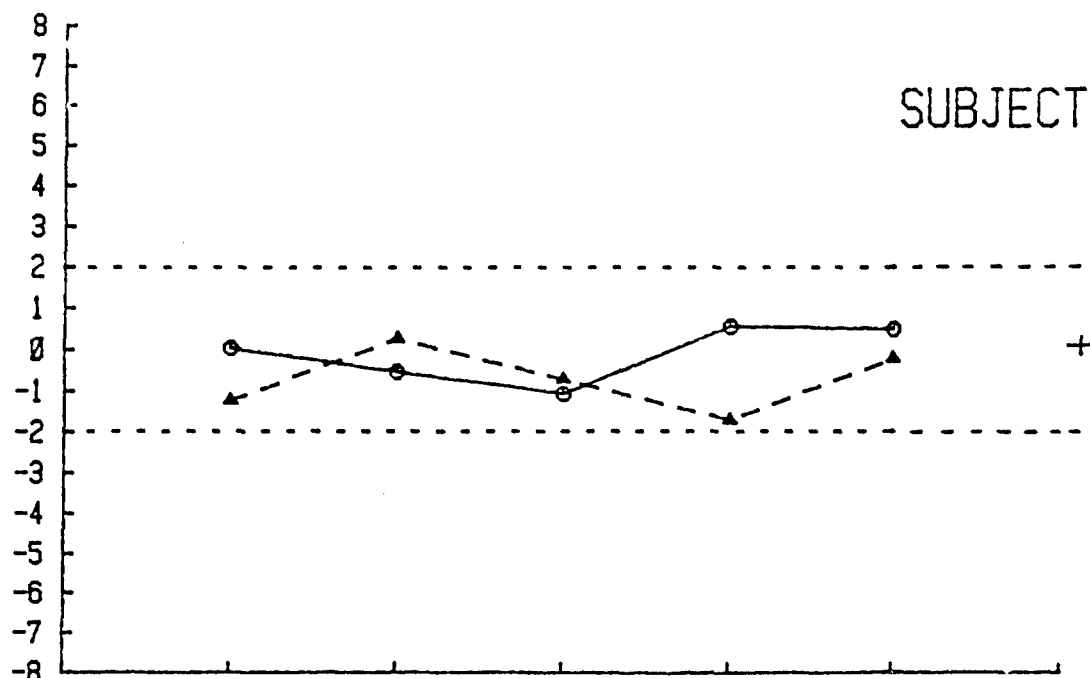
Horizontal

# PRALIDOXIME PERCENT OF TARGETS FIXATED

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○ - - - - ○ LATE

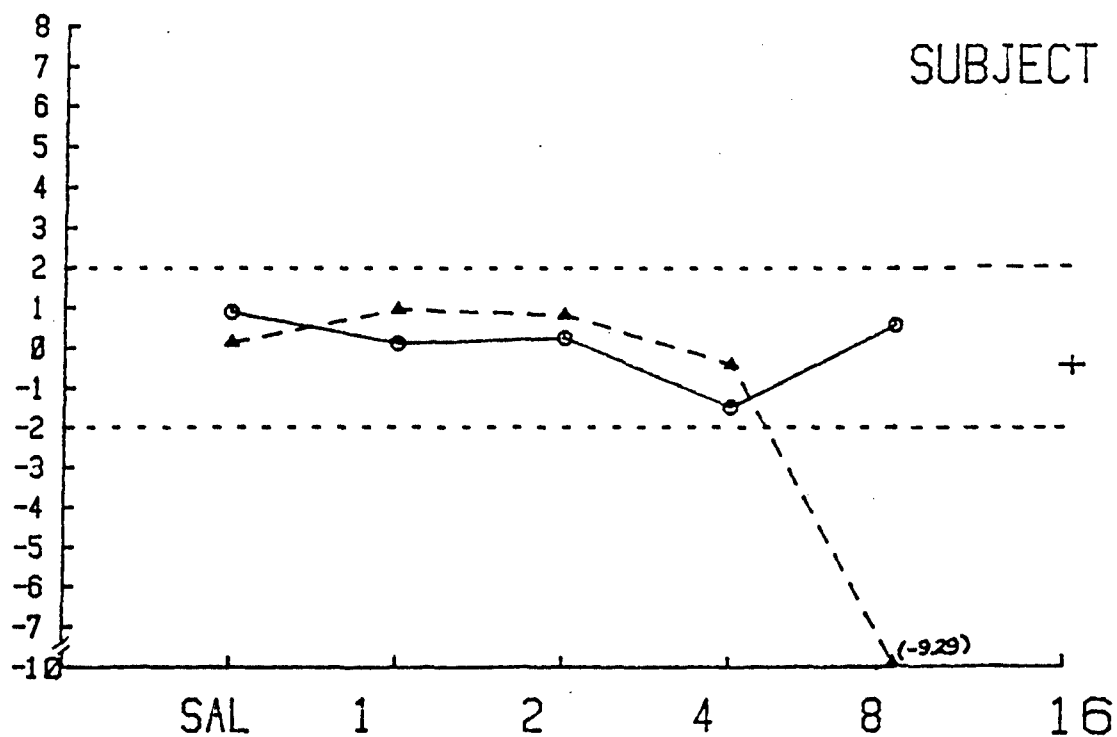
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE



MG/K

+ = TO BE COLLECTED



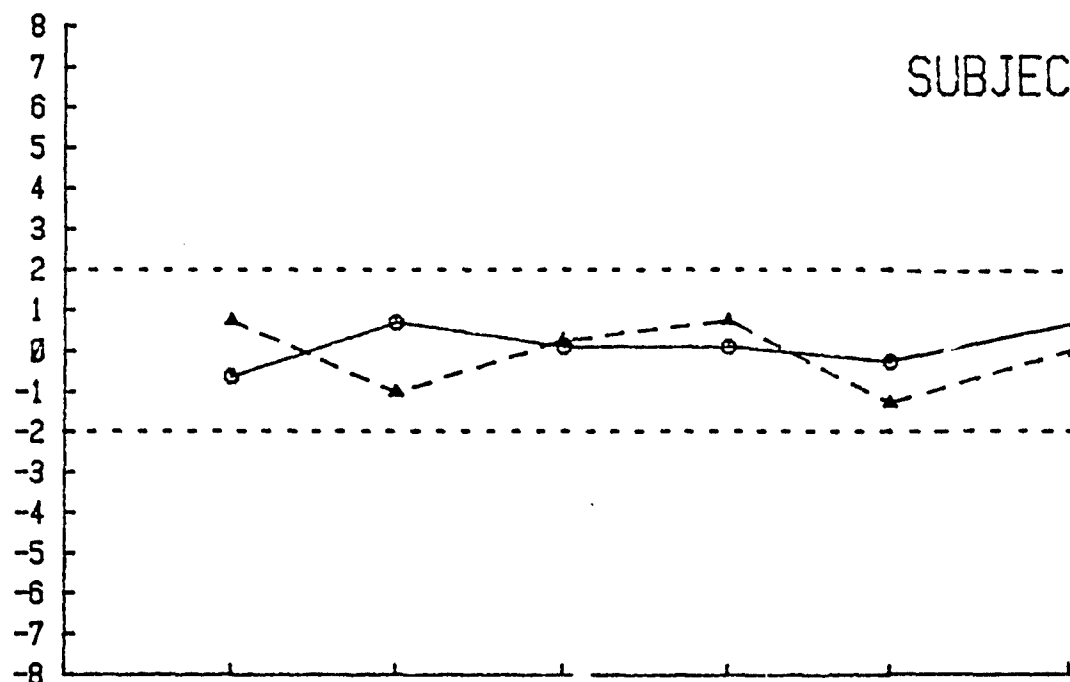
# PRALIDOXIME PERCENT OF TARGETS FIXATED

---△ EARLY

—○ LATE

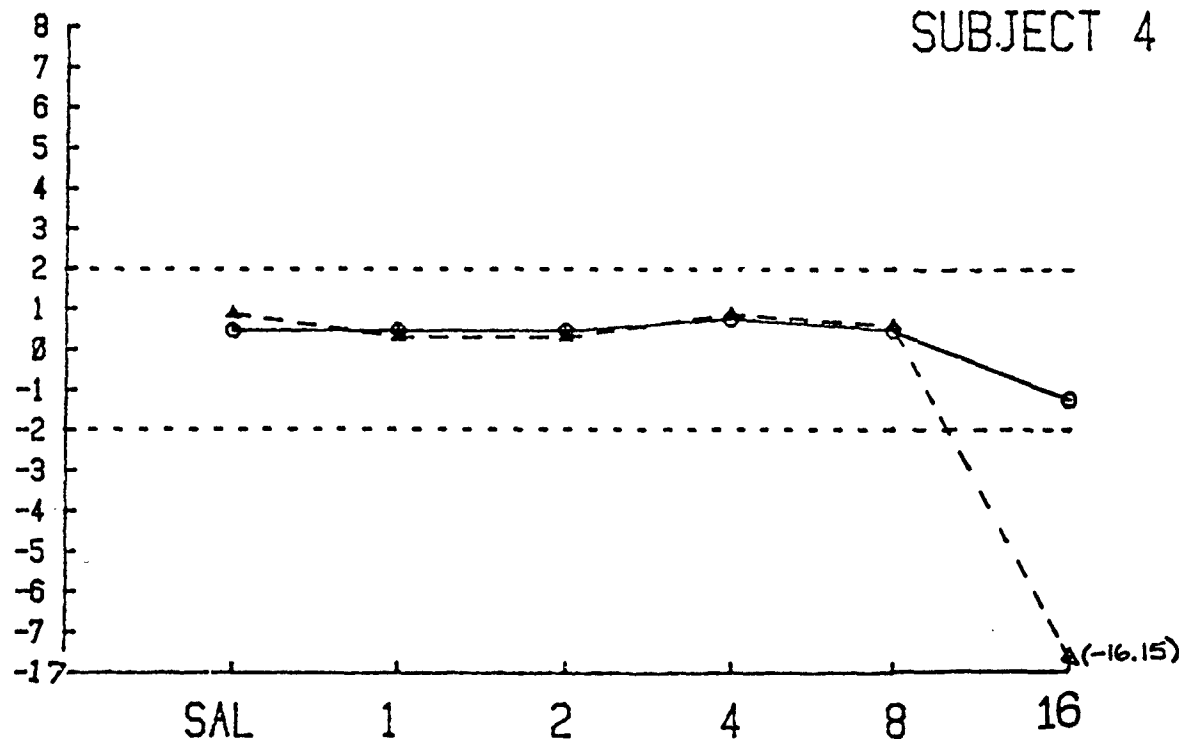
SUBJECT 3

Z SCORE



SUBJECT 4

Z SCORE



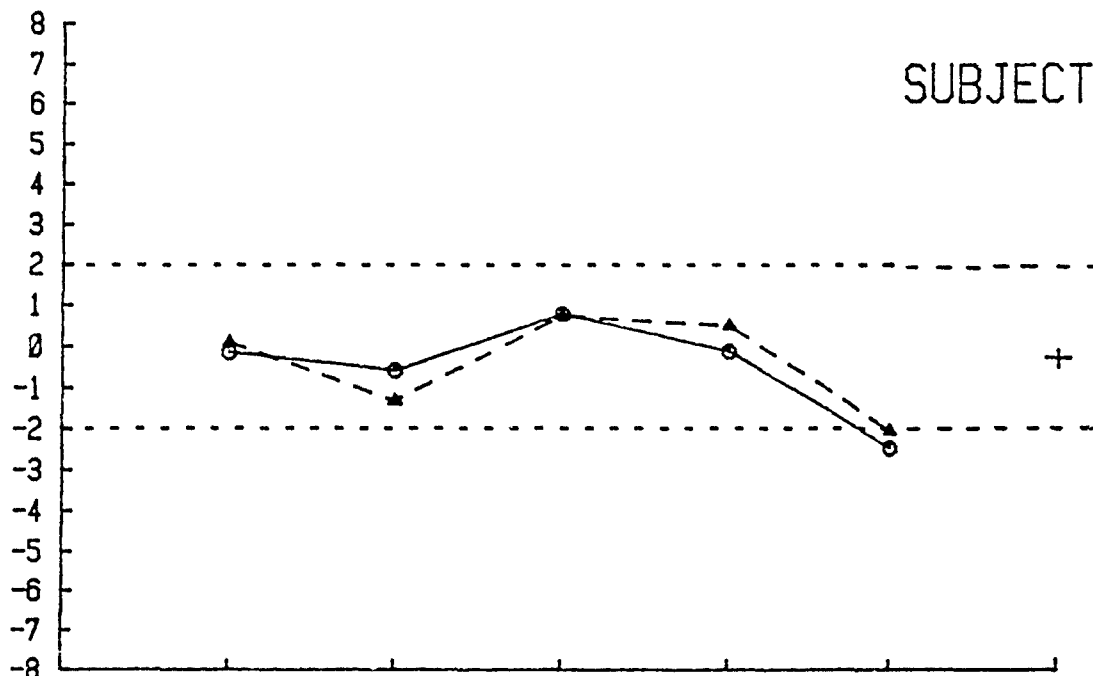
MG/K

# PRALIDOXIME TIME TO FIXATE TARGET

▲ - - - - ▲ EARLY  
○ - - - - ○ LATE

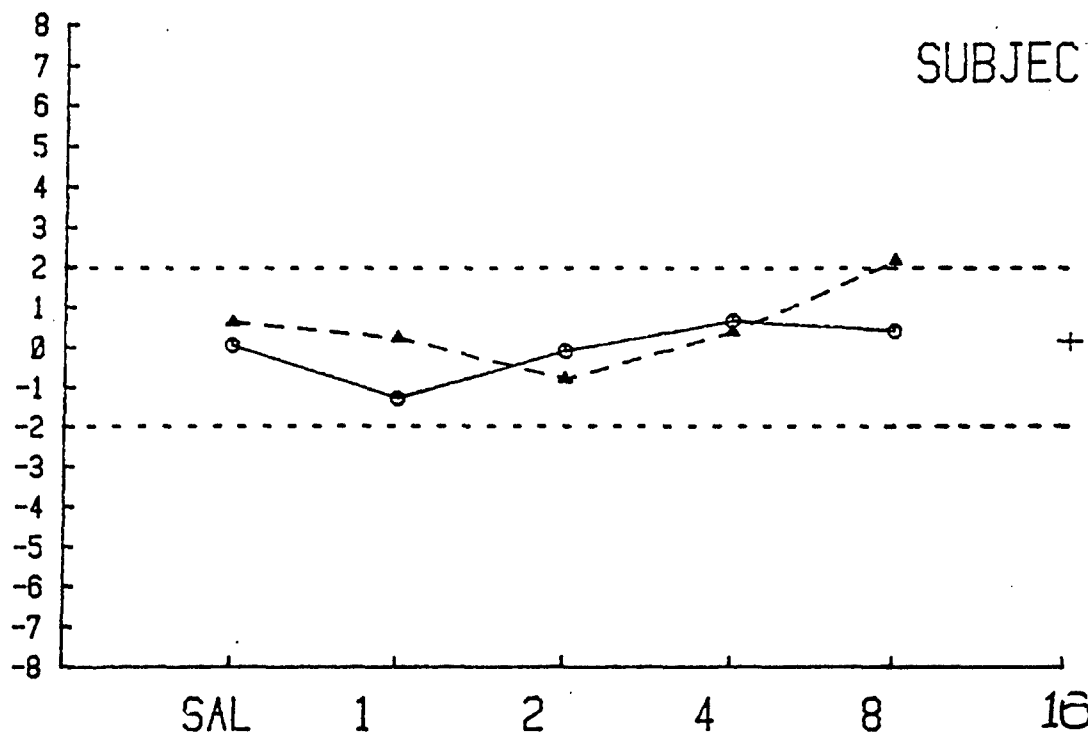
SUBJECT 1

Z SCORE



SUBJECT 2

Z SCORE



+ - TO BE COLLECTED

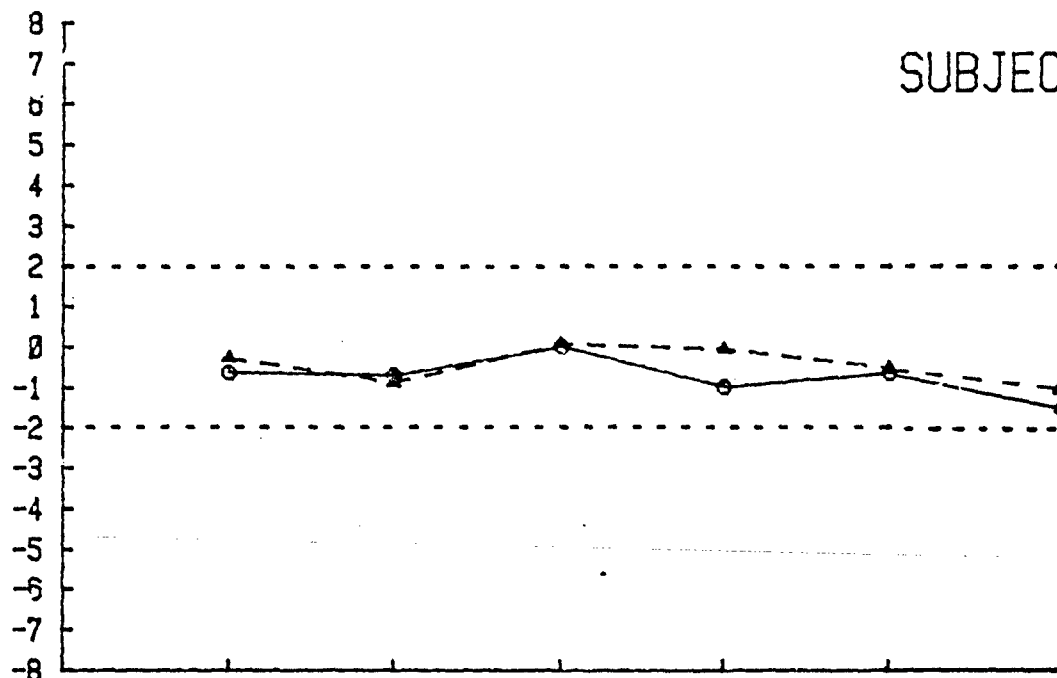
MG/K

VALIDATION  
TIME TO FIXATE TARGET

▲ --- ▲ EARLY  
○ — ○ LATE

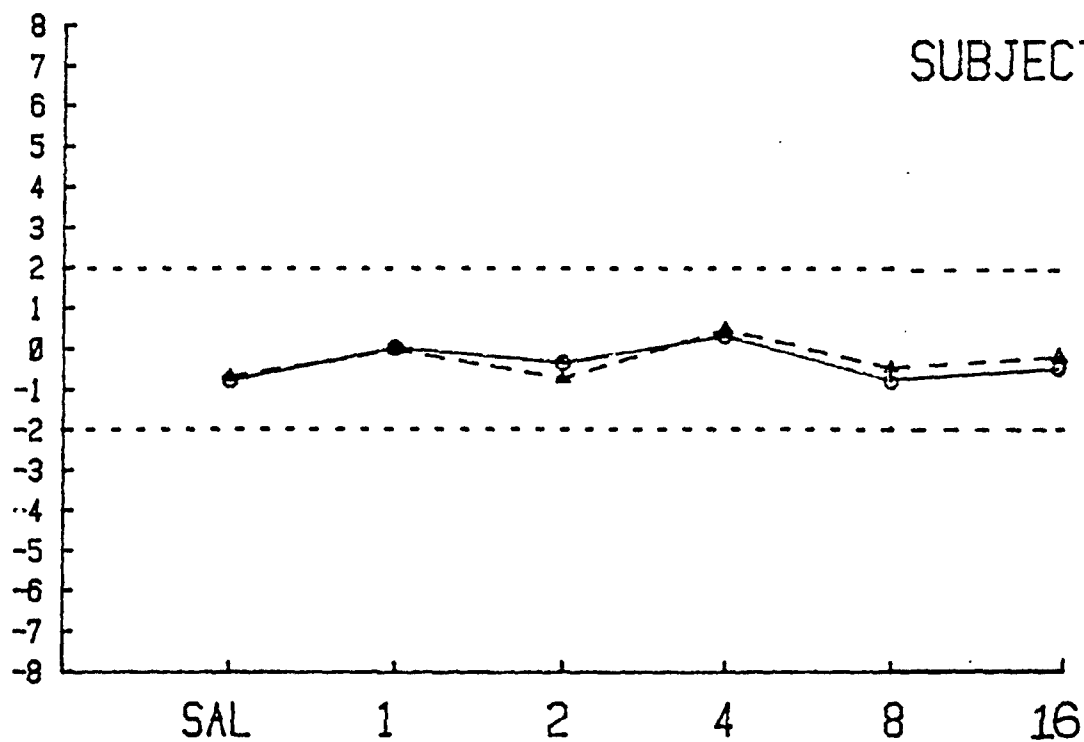
SUBJECT 3

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SUBJECT 4

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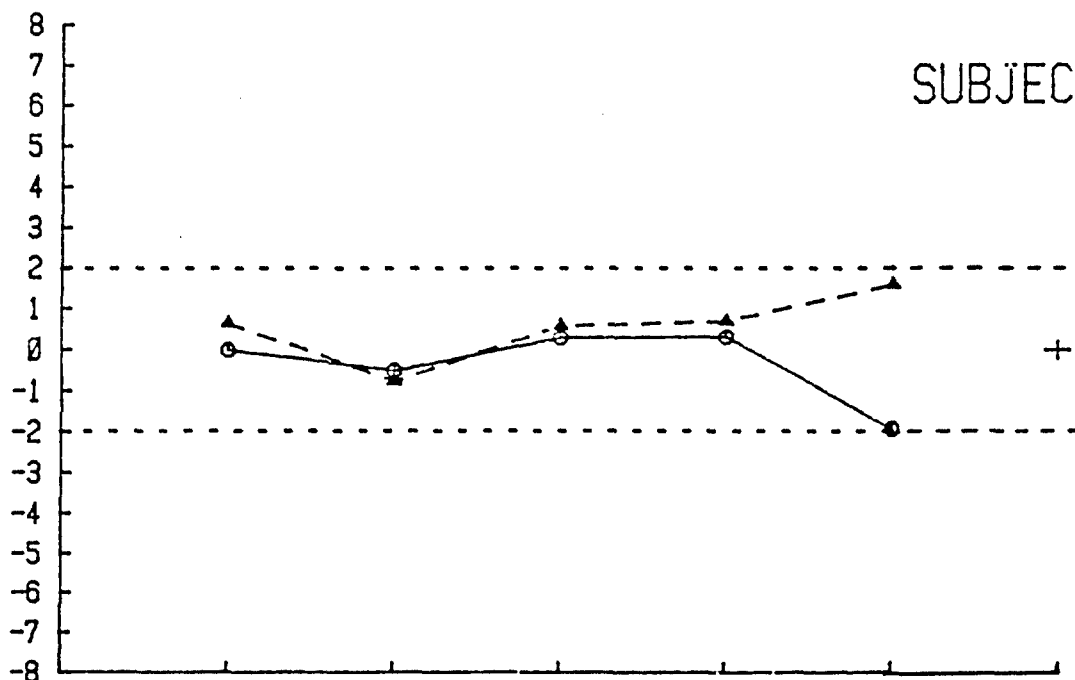
MG/K

PRALIDOXIME  
NUMBER OF FIXATIONS TO FIND TARGET

▲ - - - - ▲ EARLY  
○ - - - - ○ LATE

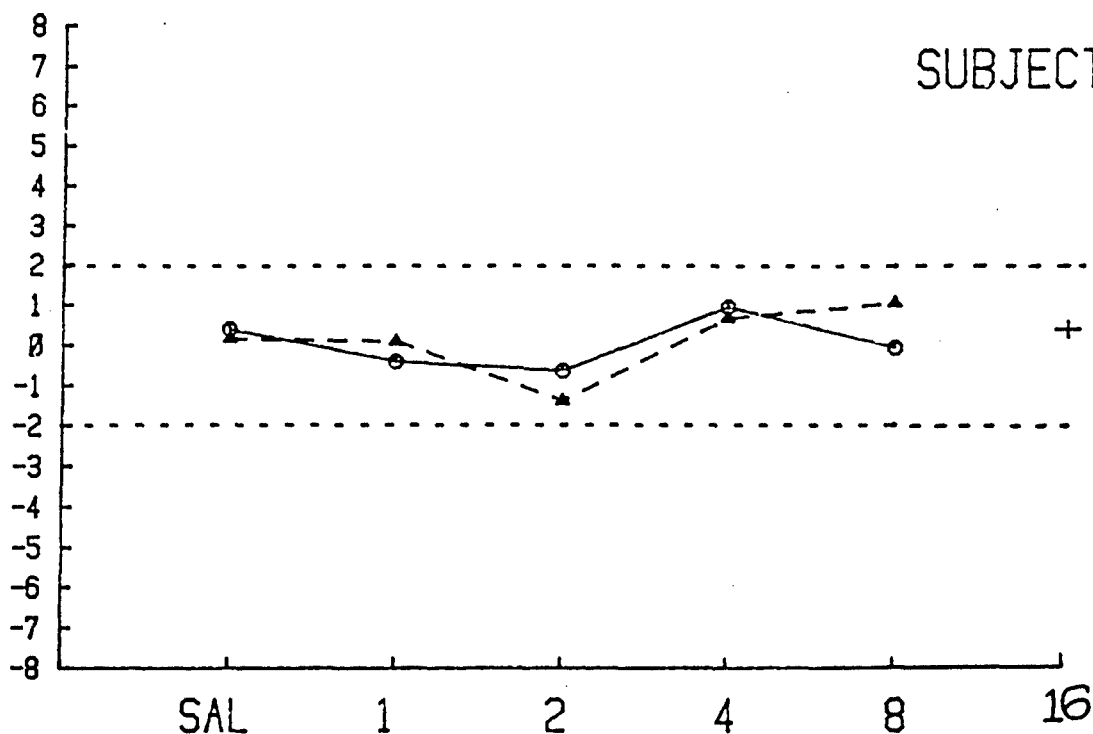
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SUBJECT 1



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SUBJECT 2



MG/K

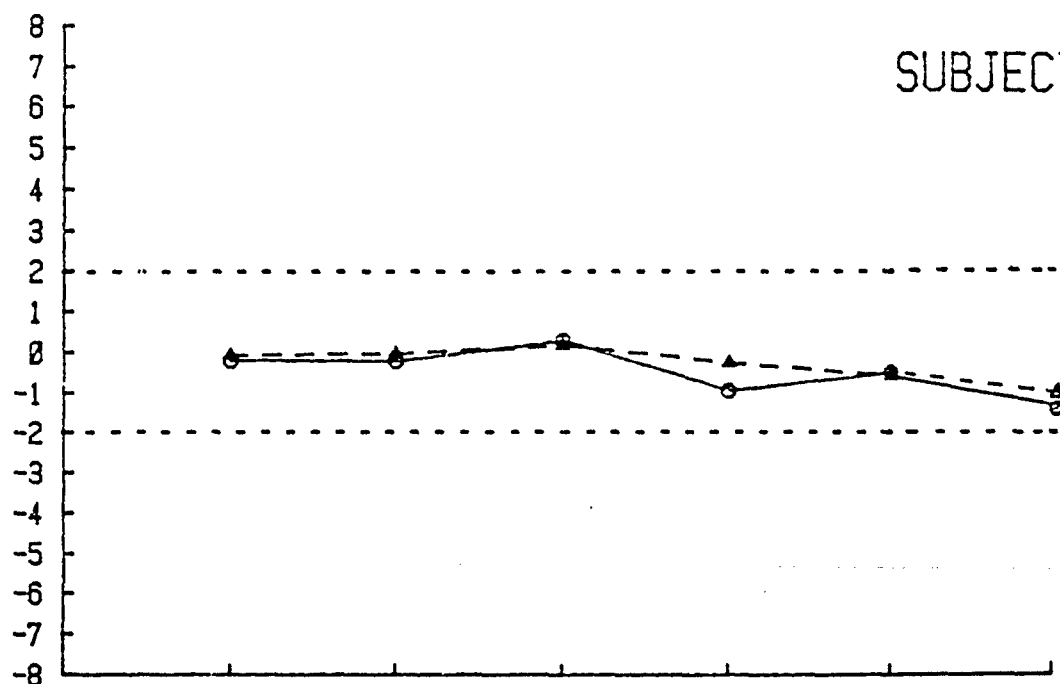
+ = TO BE COLLECTED

PRALIDOXIME  
NUMBER OF FIXATIONS TO FIND TARGET

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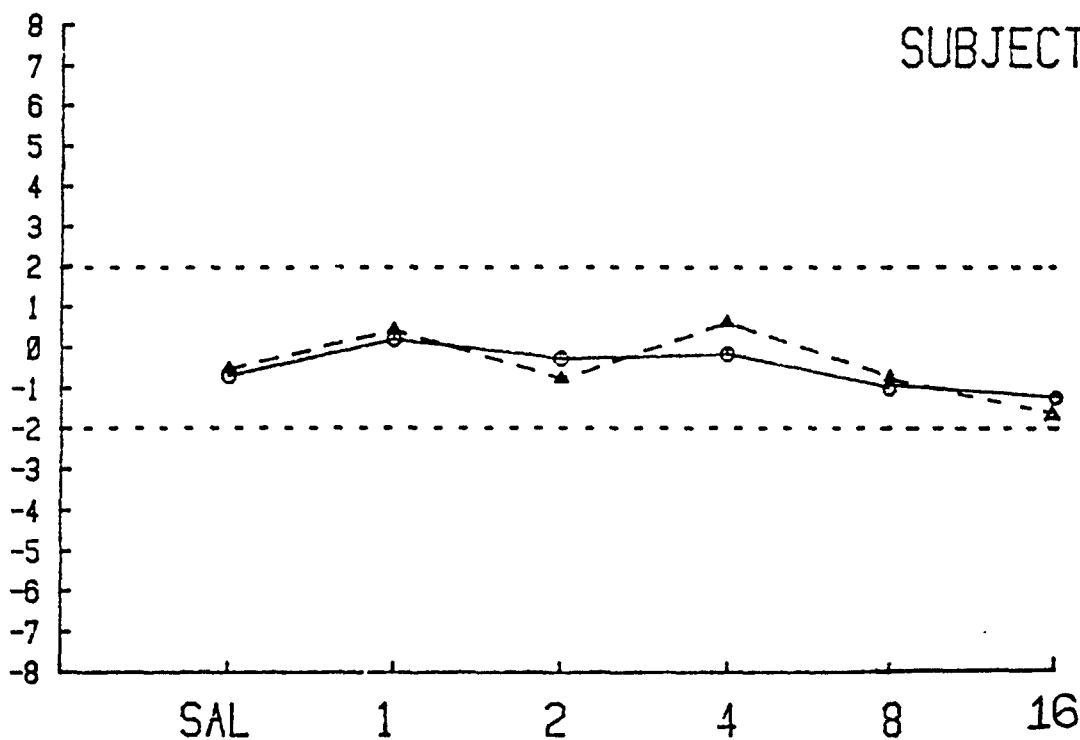
SUBJECT 3

Z SCORE



SUBJECT 4

Z SCORE



MG/K

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END

DATE

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